Figure 1: Sedation Model

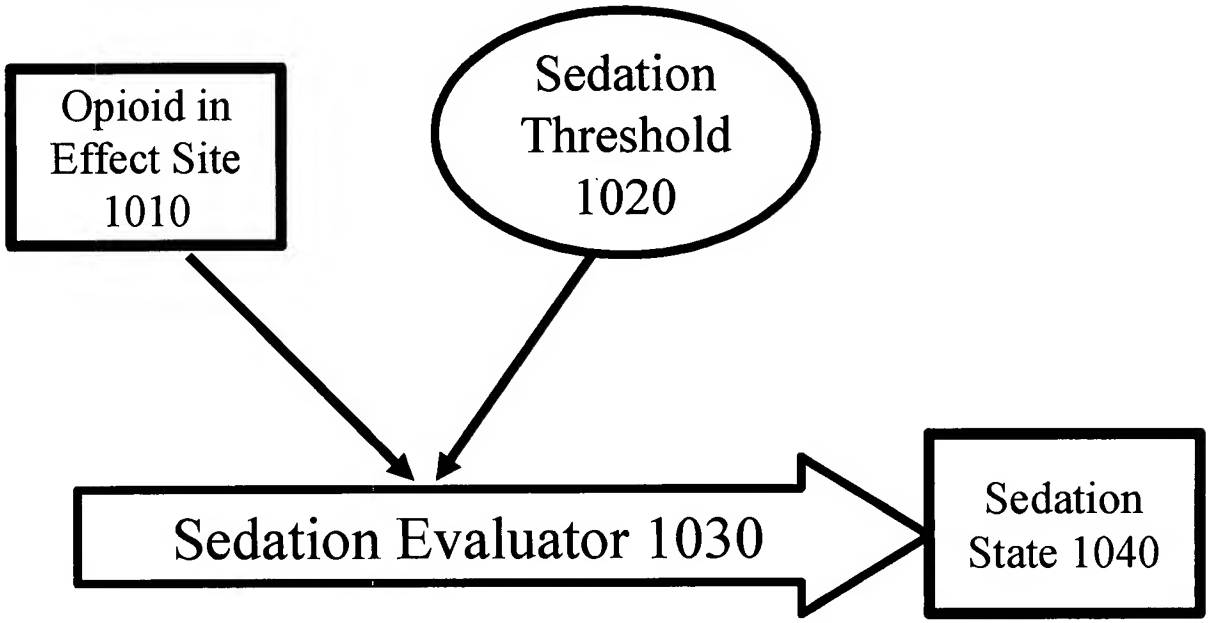


Figure 2: Ventilatory Depression Model

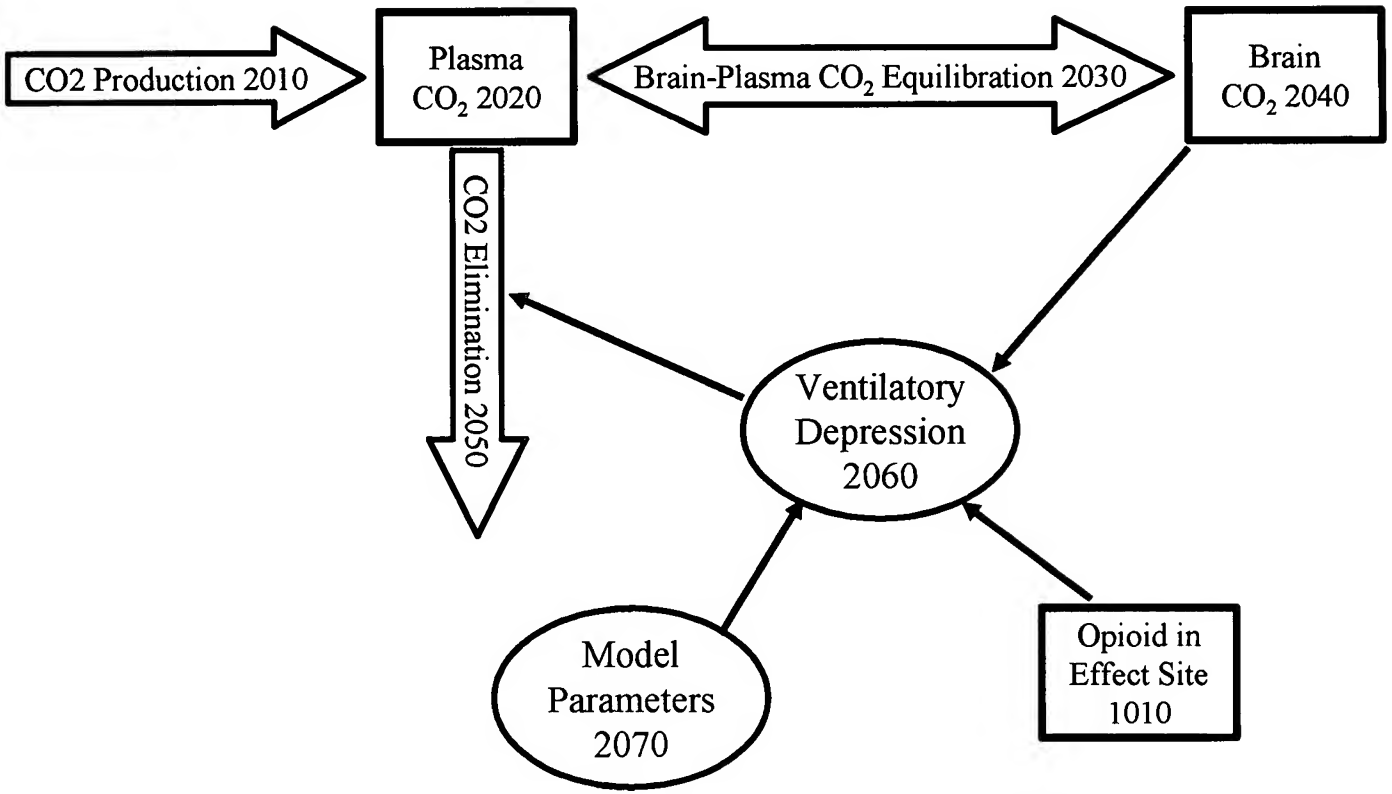


Figure 3: Device Model

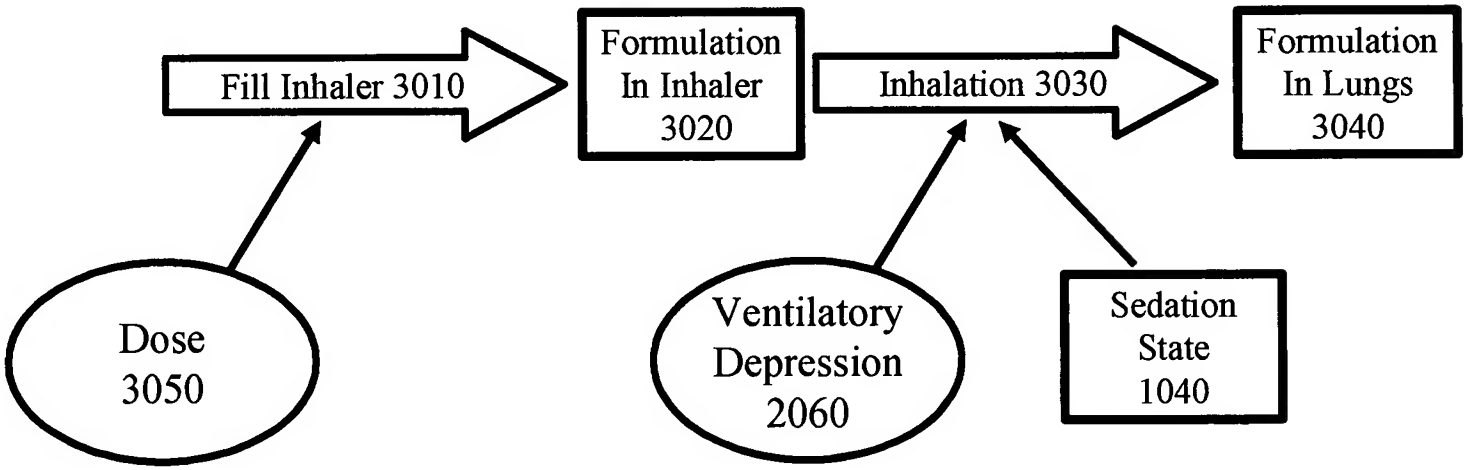


Figure 4: Pharmacokinetic Model

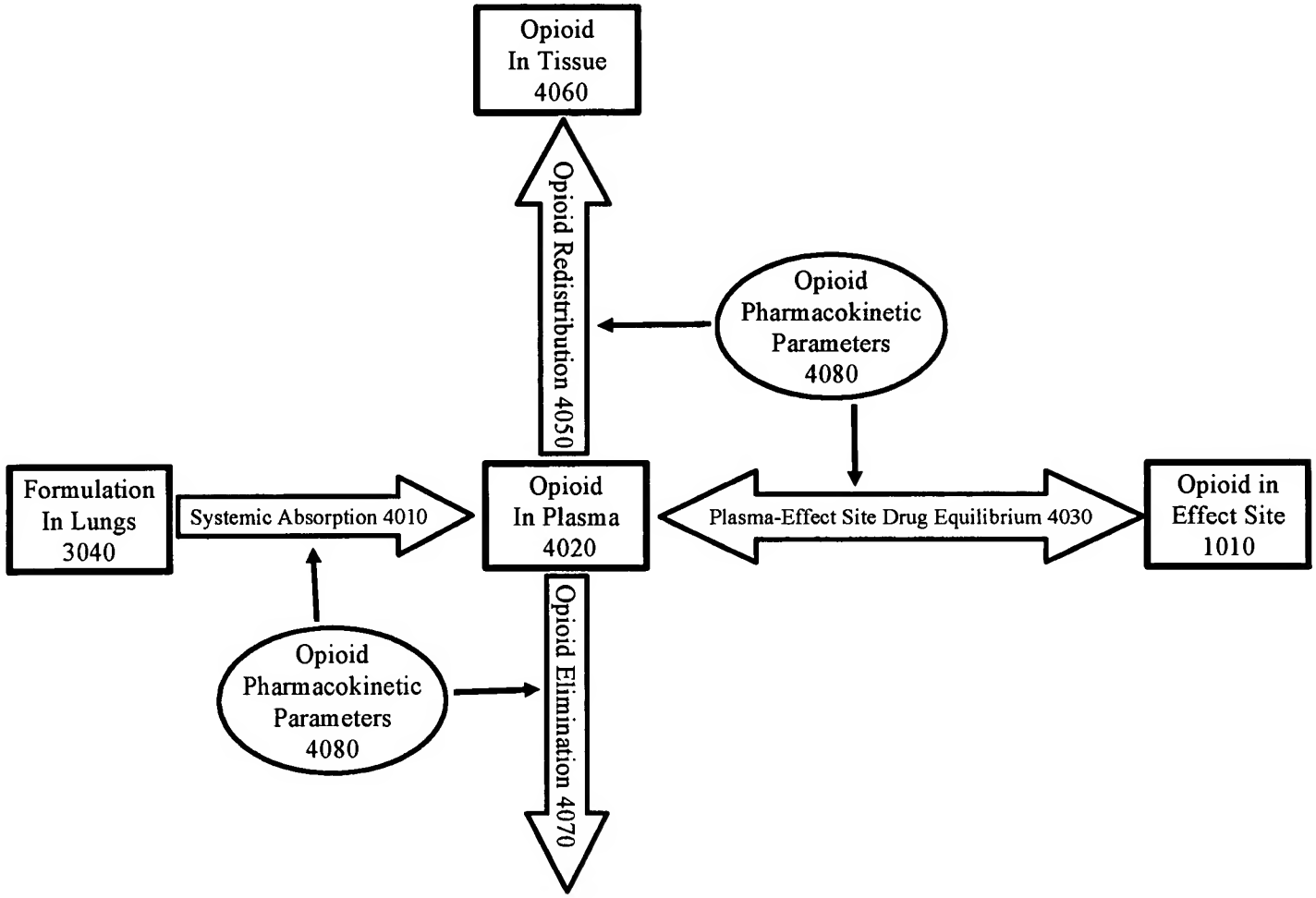


Figure 5A

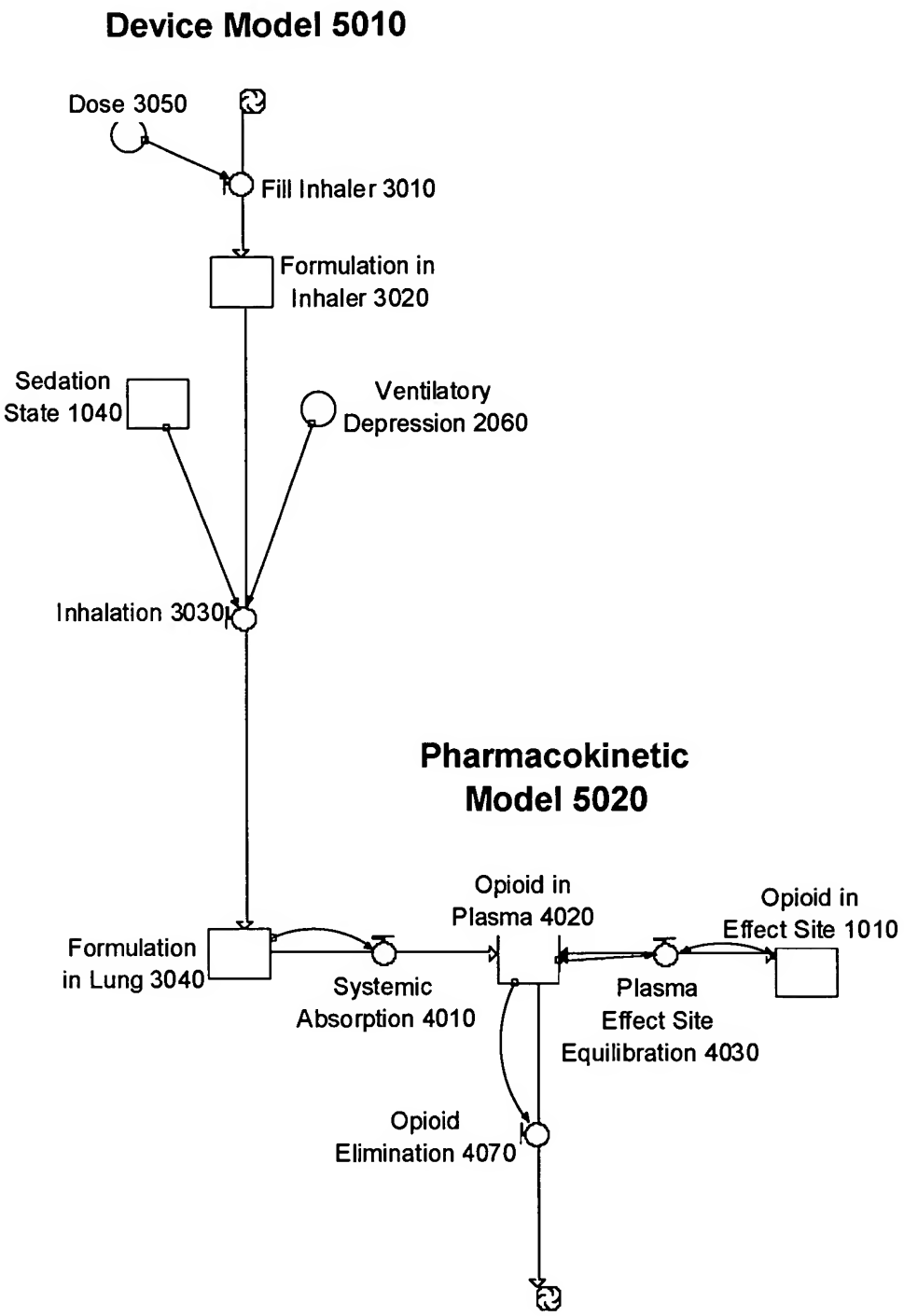

Device Model 5010
Dose 3050
Fill Inhaler 3010
Formulation in Inhaler 3020
Sedation State 1040
Ventilatory Depression 2060
Inhalation 3030
Pharmacokinetic Model 5020
Opioid in Plasma 4020
Opioid in Effect Site 1010
Formulation in Lung 3040
Systemic Absorption 4010
Plasma Effect Site Equilibration 4030
Opioid Elimination 4070

Figure 5B

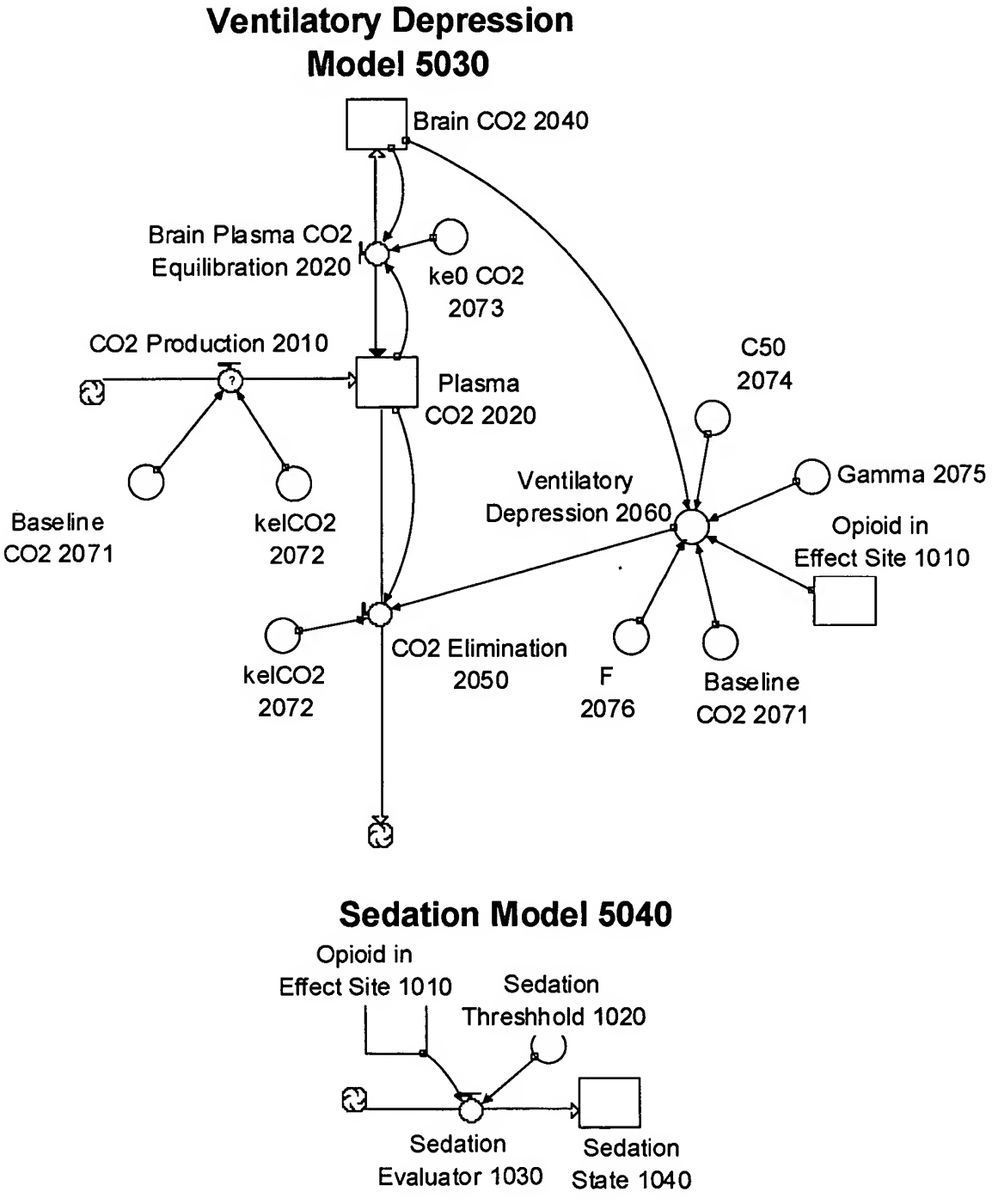

Ventilatory Depression Model 5030
Brain CO2 2040
Brain Plasma CO2 Equilibration 2020
ke0 CO2 2073
CO2 Production 2010
Plasma CO2 2020
C50 2074
Gamma 2075
Ventilatory Depression 2060
Opioid in Effect Site 1010
Baseline CO2 2071
kelCO2 2072
CO2 Elimination 2050
kelCO2 2072
F 2076
Baseline CO2 2071
Sedation Model 5040
Opioid in Effect Site 1010
Sedation Threshhold 1020
Sedation Evaluator 1030
Sedation State 1040

Figure 6

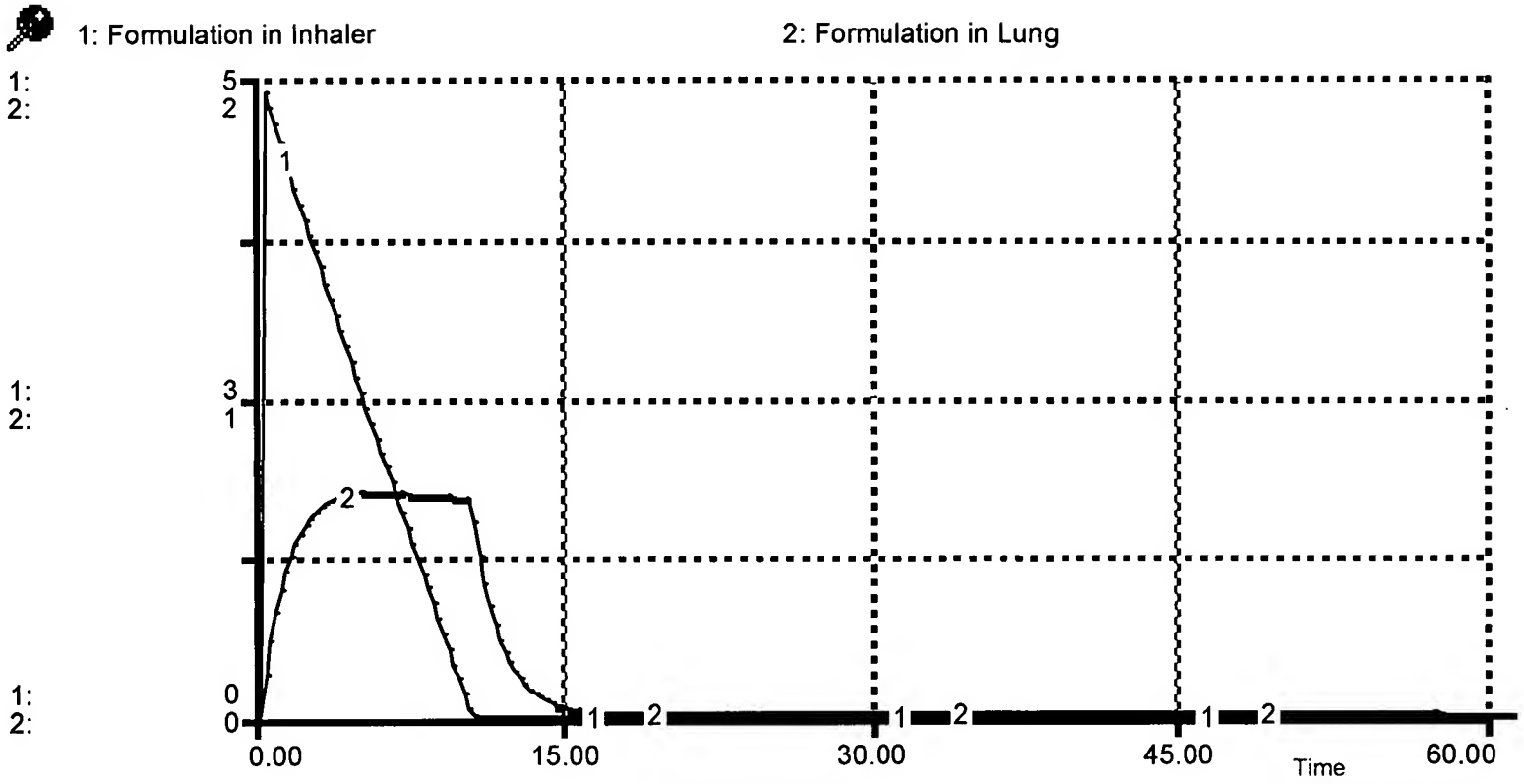

1: Formulation in Inhaler
2: Formulation in Lung
1:
2:
5
2
1
1:
2:
3
1
2
1:
2:
0
0
1
2
1
2
1
2
0.00
15.00
30.00
45.00
60.00
Time

Figure 7

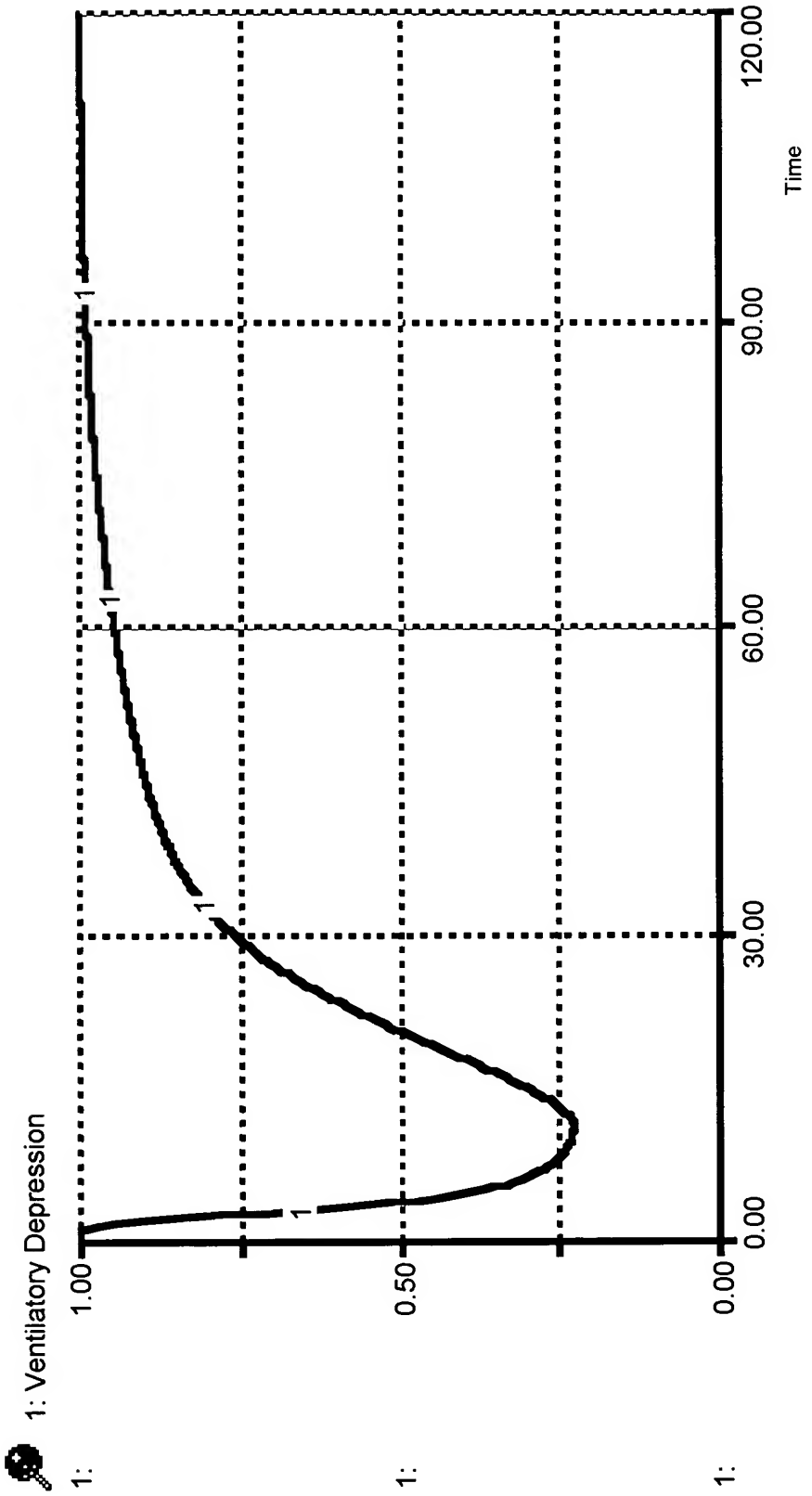

1: Ventilatory Depression
1:
1:
1:
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 8

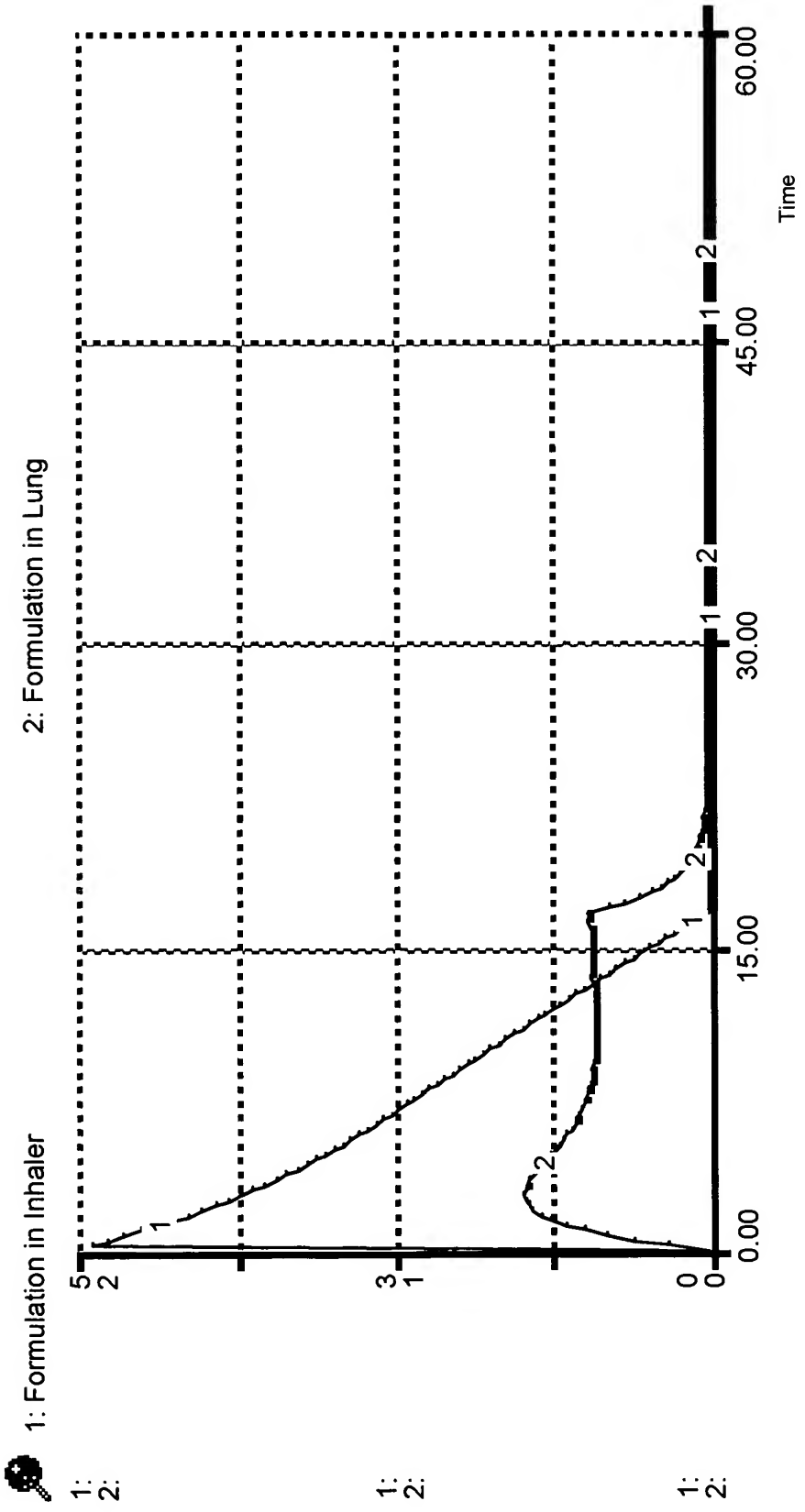

1: Formulation in Inhaler
2: Formulation in Lung
1:
2:
1:
2:
1:
2:
5
2
3
1
0
0
0.00
15.00
30.00
45.00
60.00
Time

Figure 9

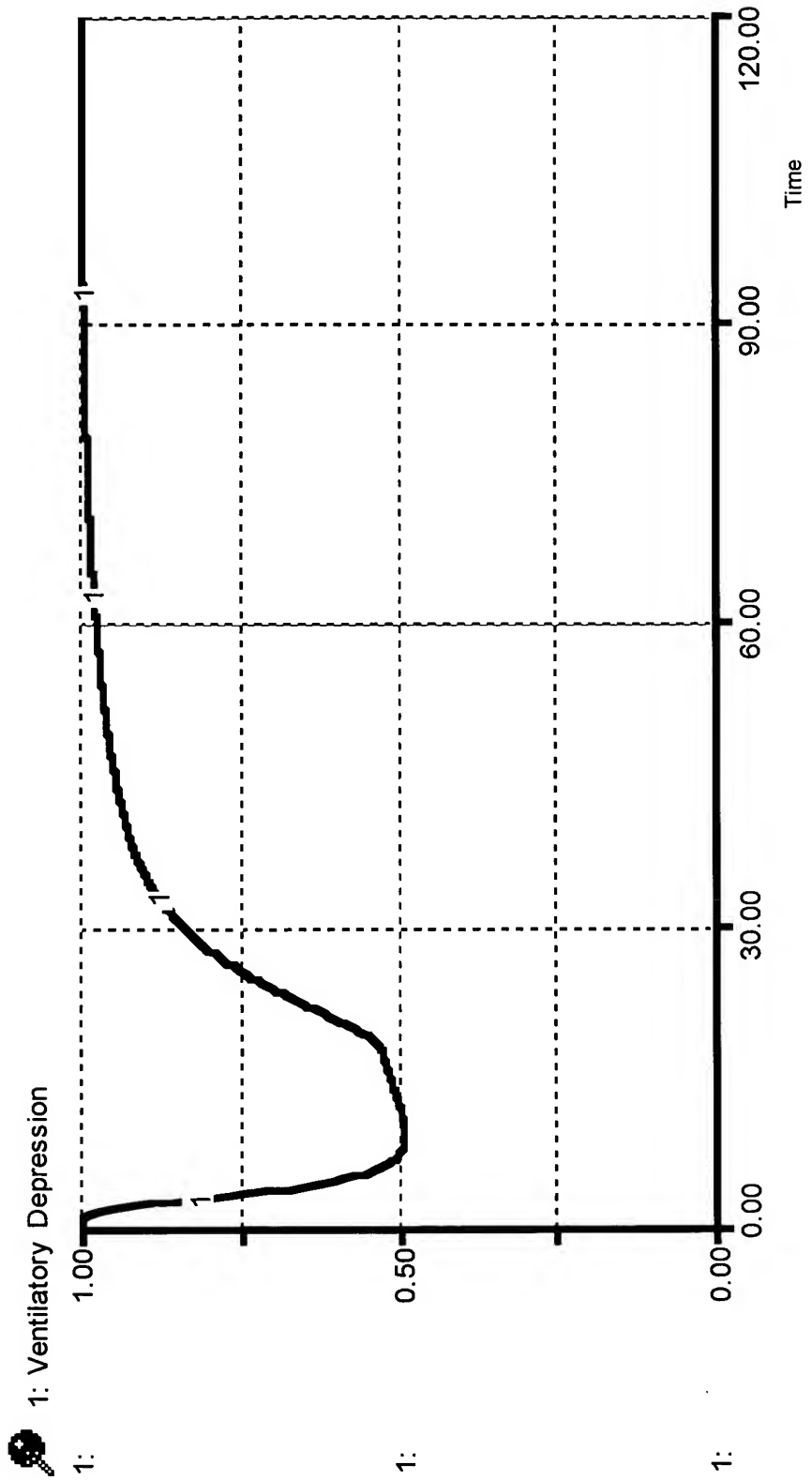

1: Ventilatory Depression
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 10

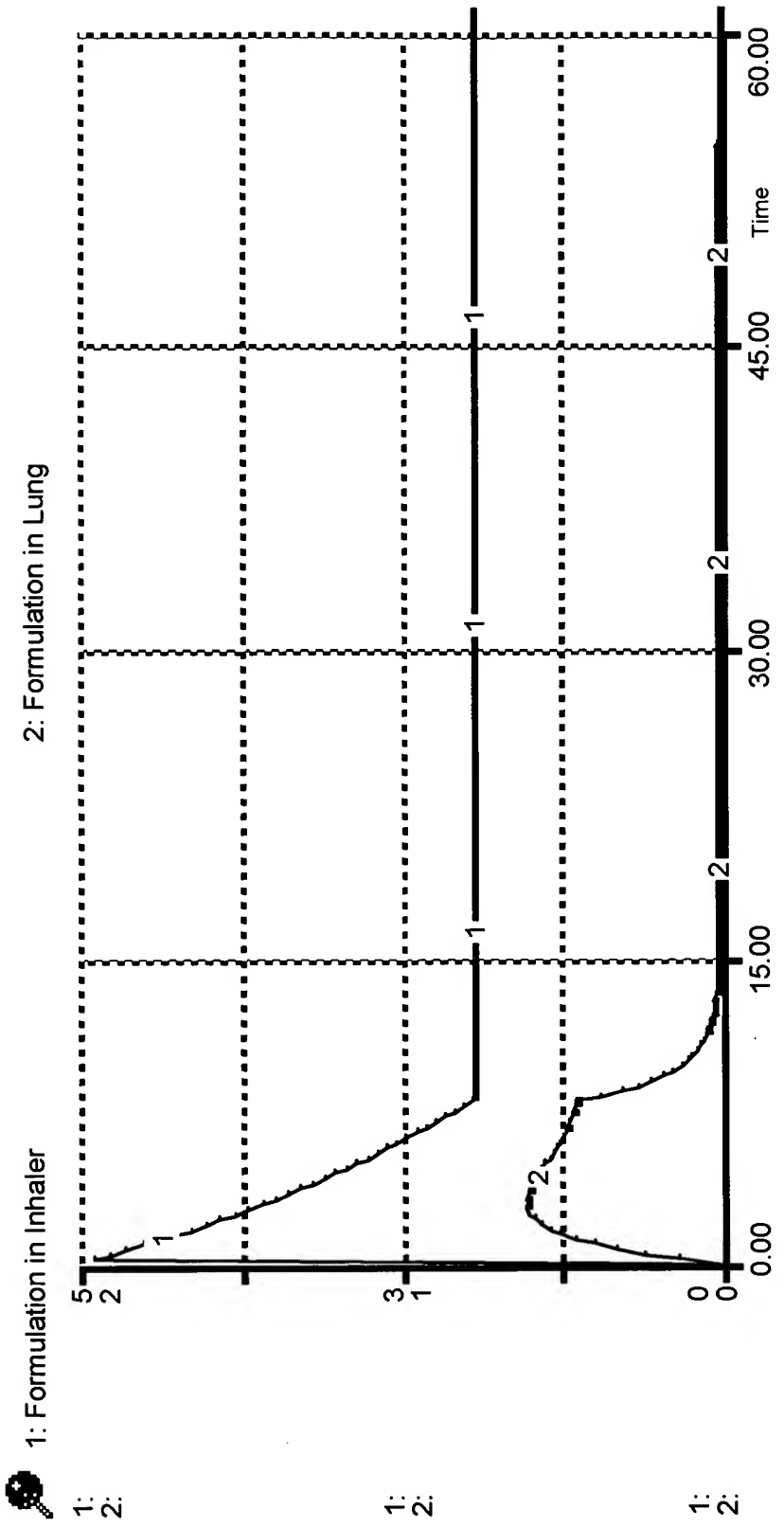

1: Formulation in Inhaler
2: Formulation in Lung
1:
2:
5
2
3
1
0
0
0.00
15.00
30.00
45.00
60.00
Time

Figure 11

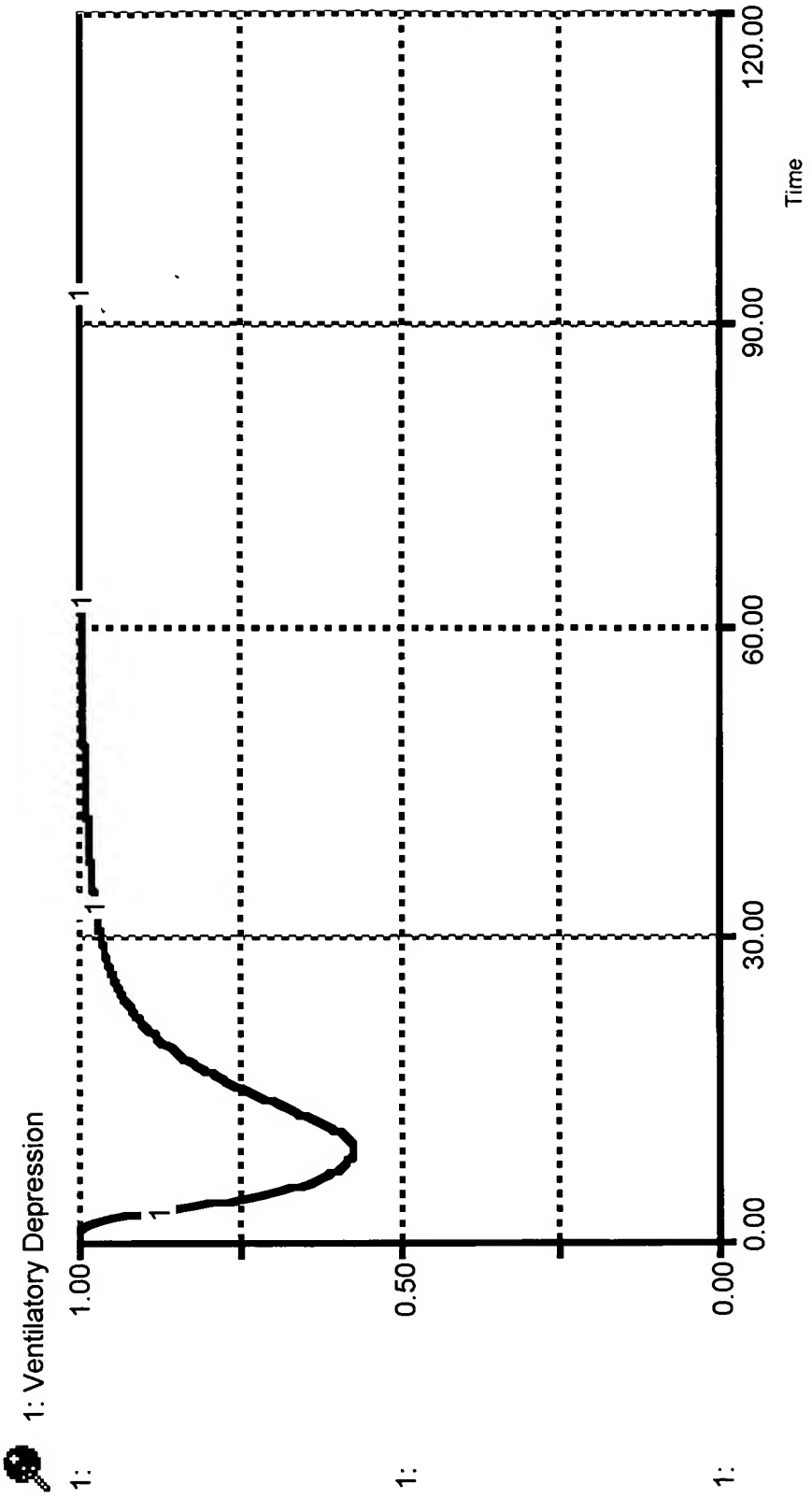

1: Ventilatory Depression
1.00
0.50
0.00
0.00
30.00
60.00
90.00
120.00
Time

Figure 12: Two Opioid Model

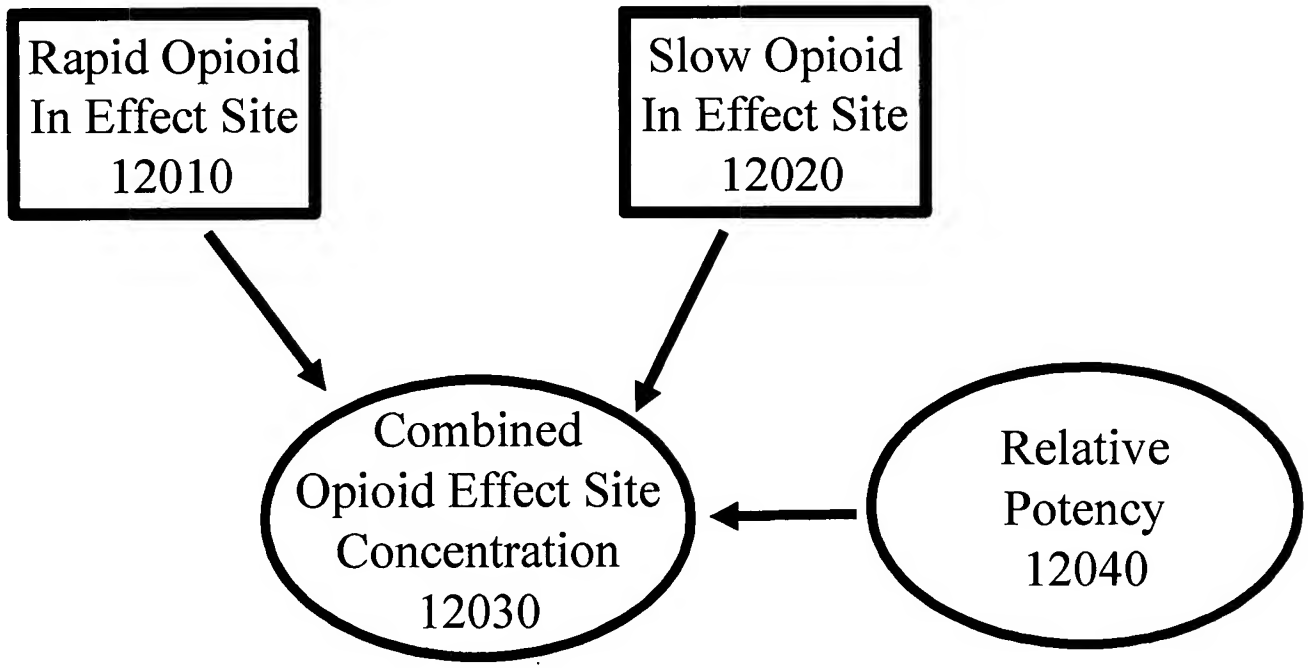


Figure 13A: The elements of the invention, wherein two opioids are administered through inhalation.

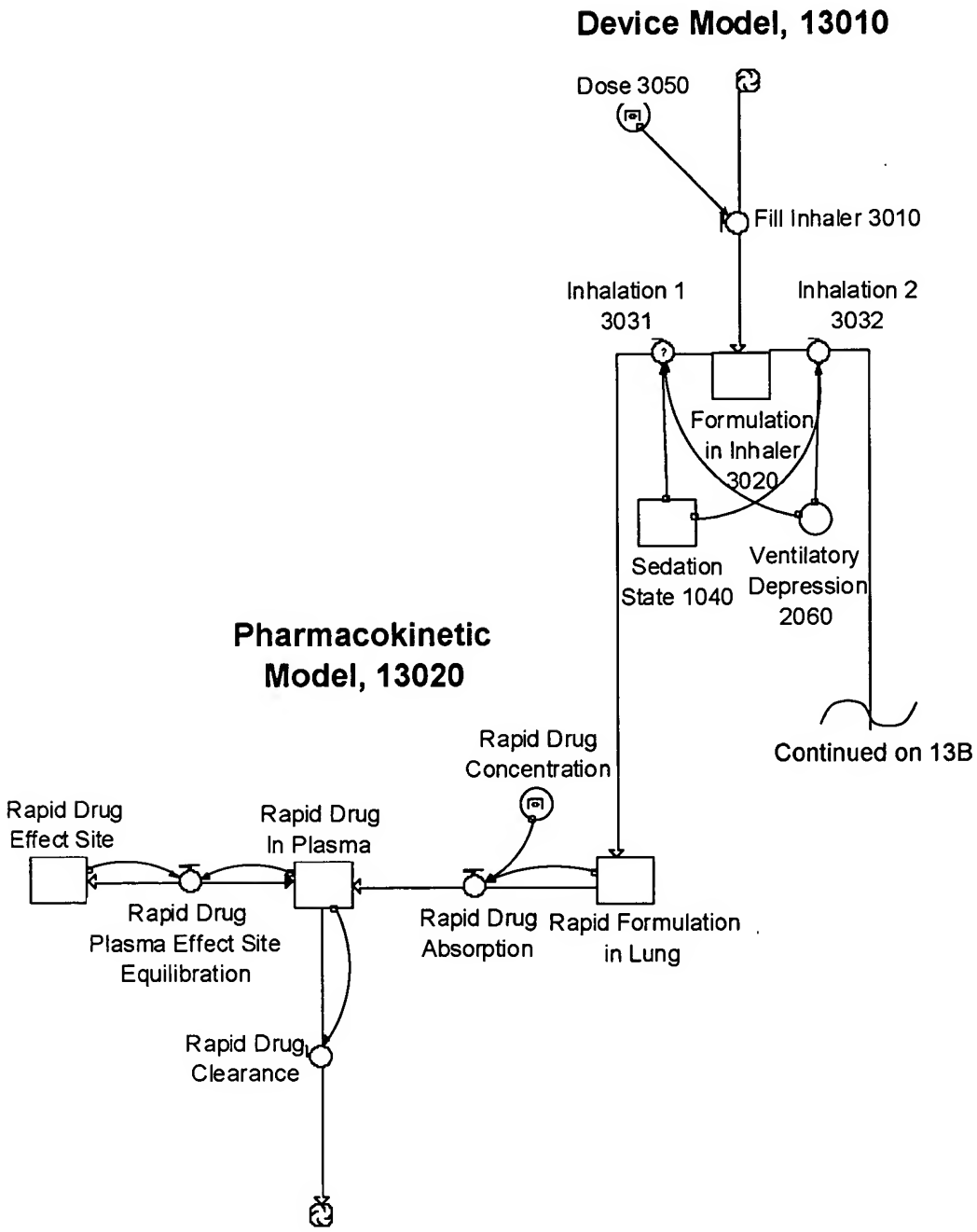


Figure 13B The elements of the invention, wherein two opioids are administered through inhalation.

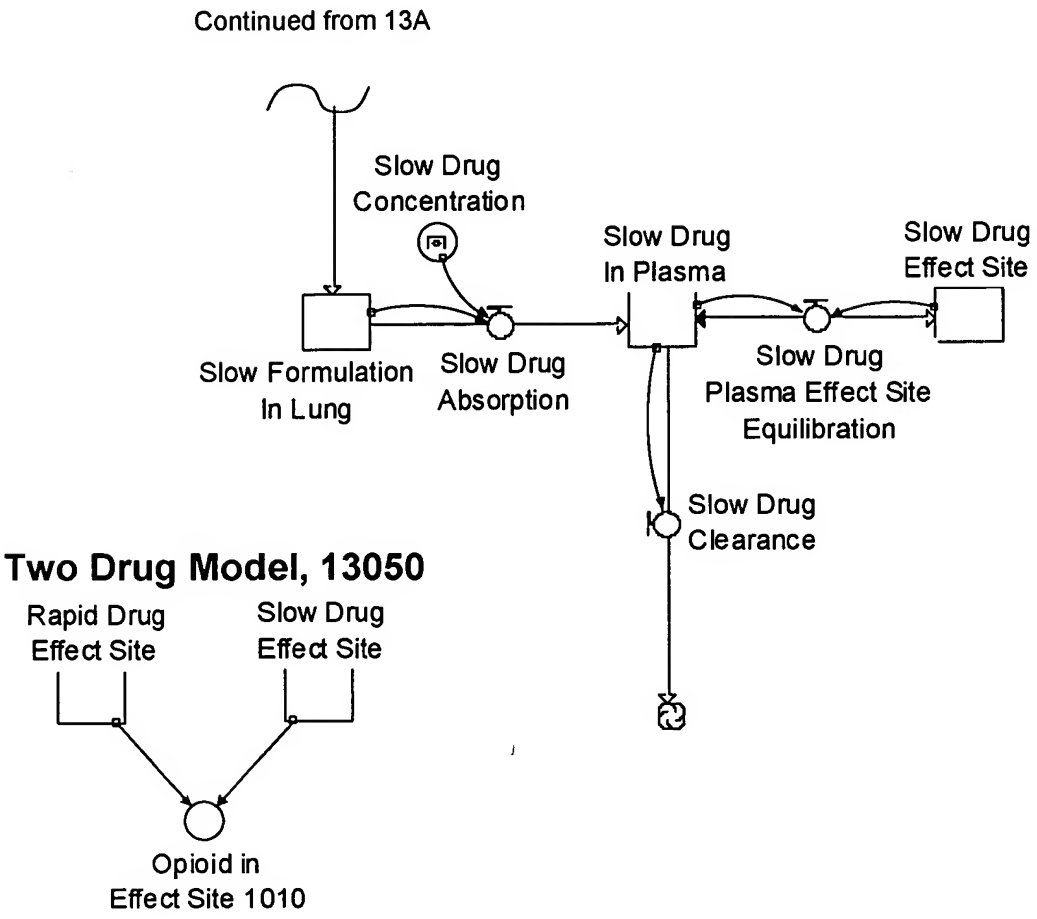
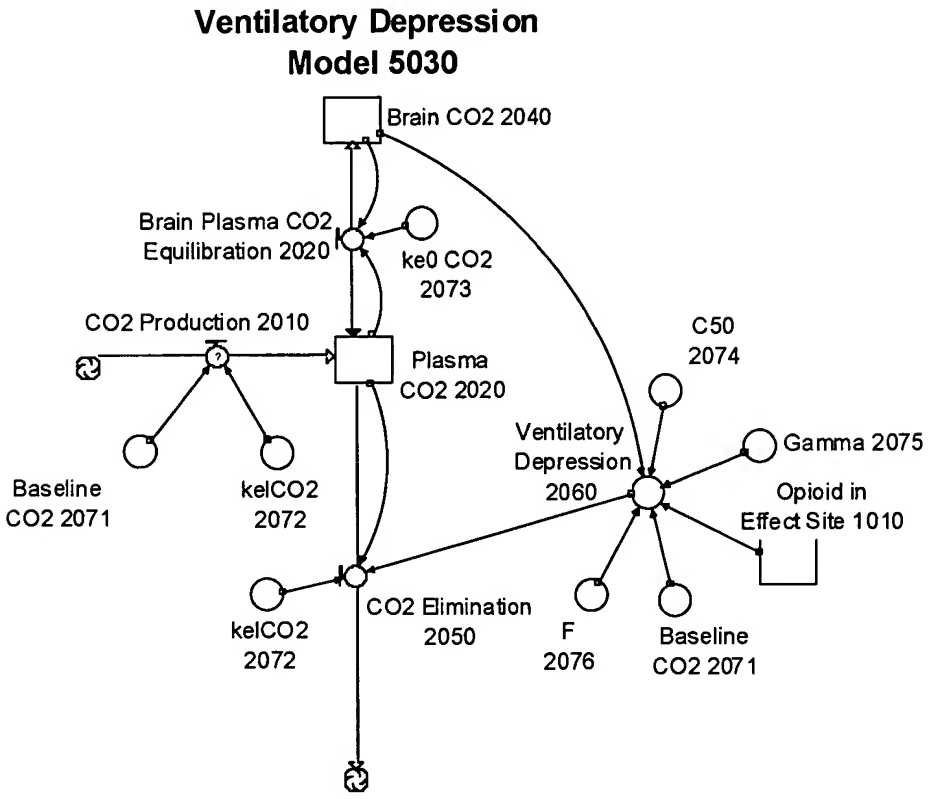


Figure 13C The elements of the invention, wherein two opioids are administered through inhalation.



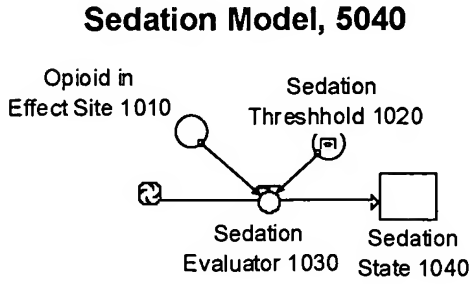


Figure 14: Drug in inhaler and lung in the presence of opioid-induced ventilatory depression and sedation for the two opioid model.

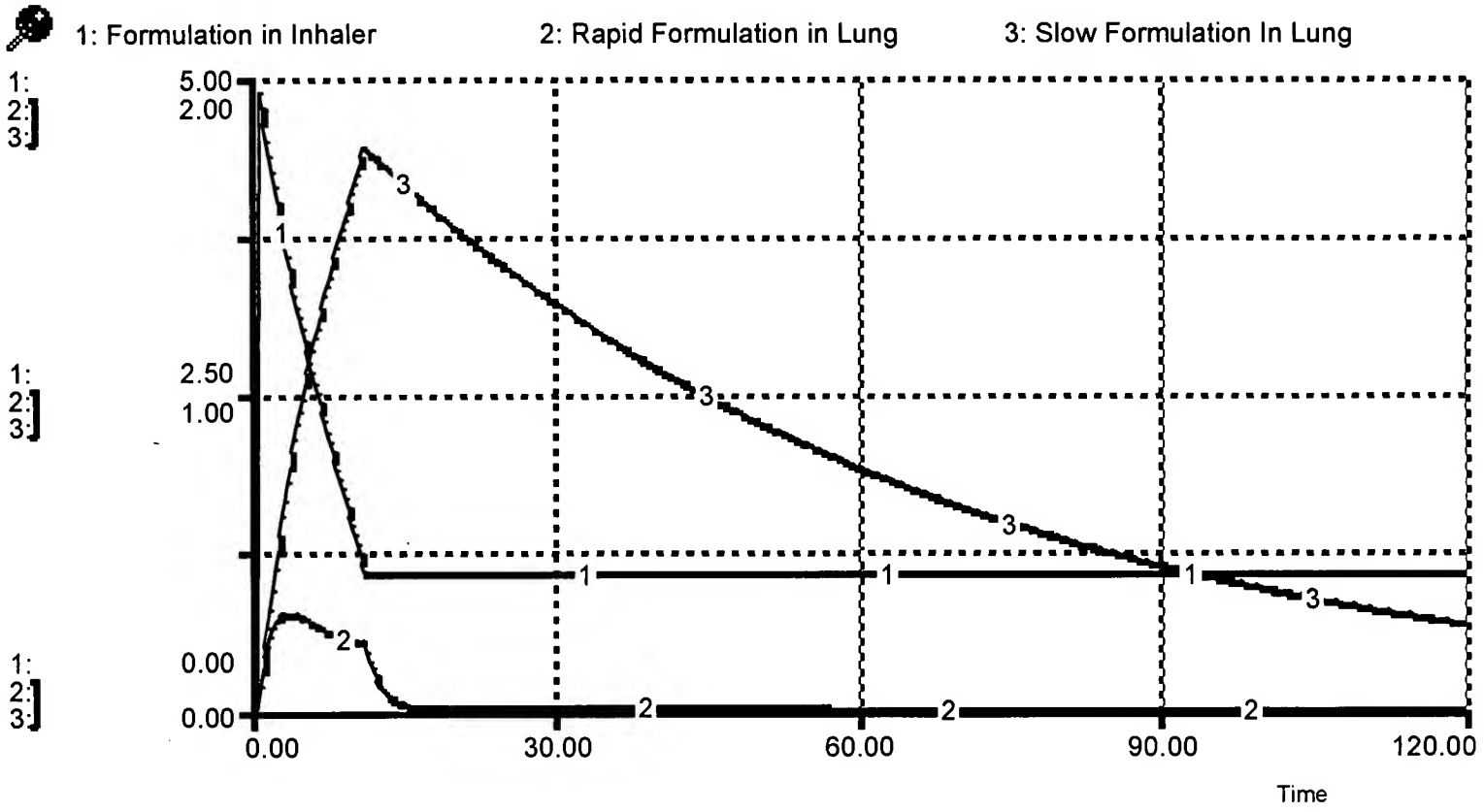


Figure 15: The rapidly acting opioid concentration in the effect site, the slowly acting opioid concentration in the effect site, and the combined concentration of opioid at the effect site, during two opioid administration with the device.

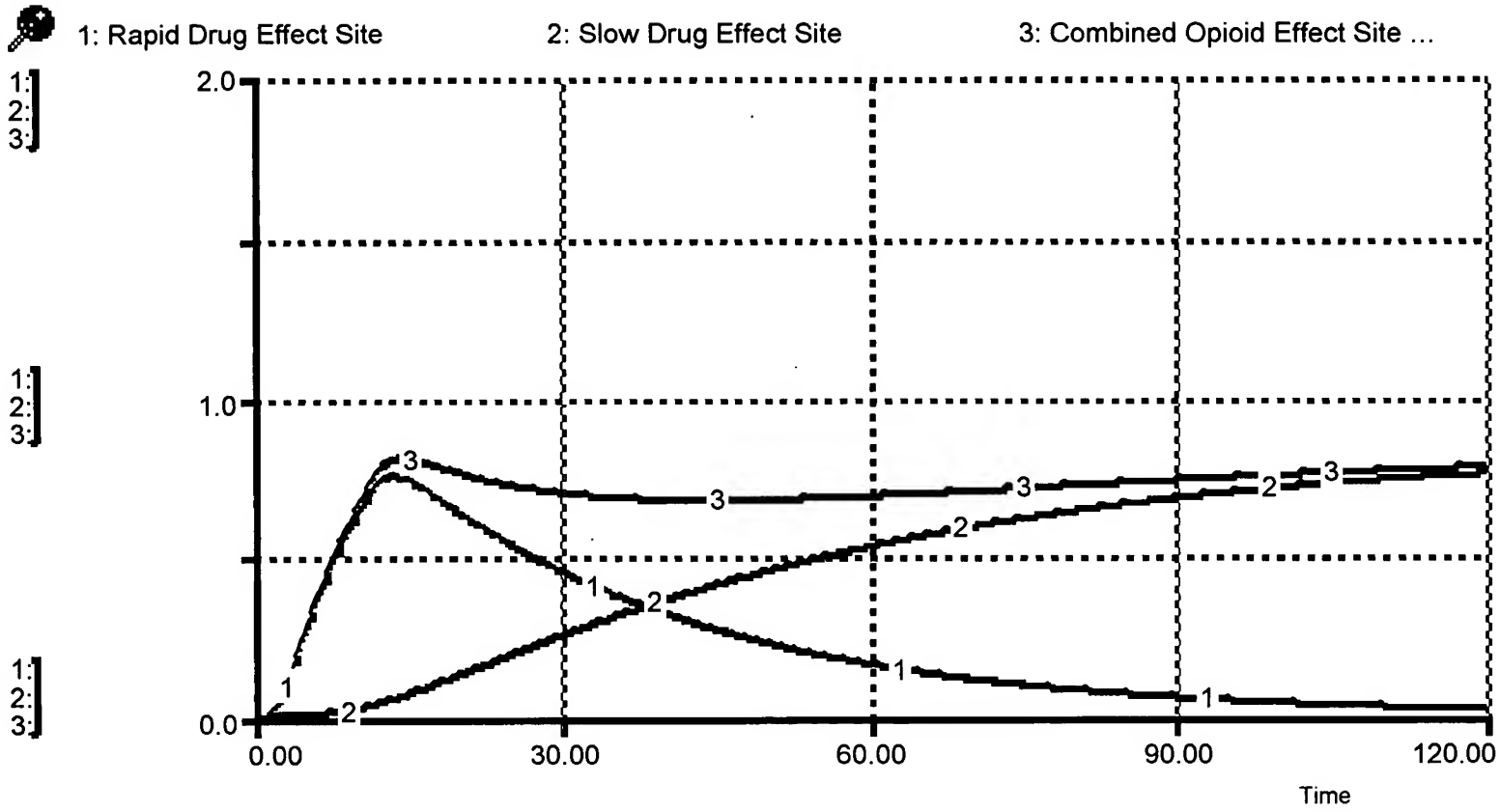


Figure 16: Ventilatory depression in the presence of self-limitation of opioid delivery from ventilatory depression and sedation with the two-opioid delivery system.

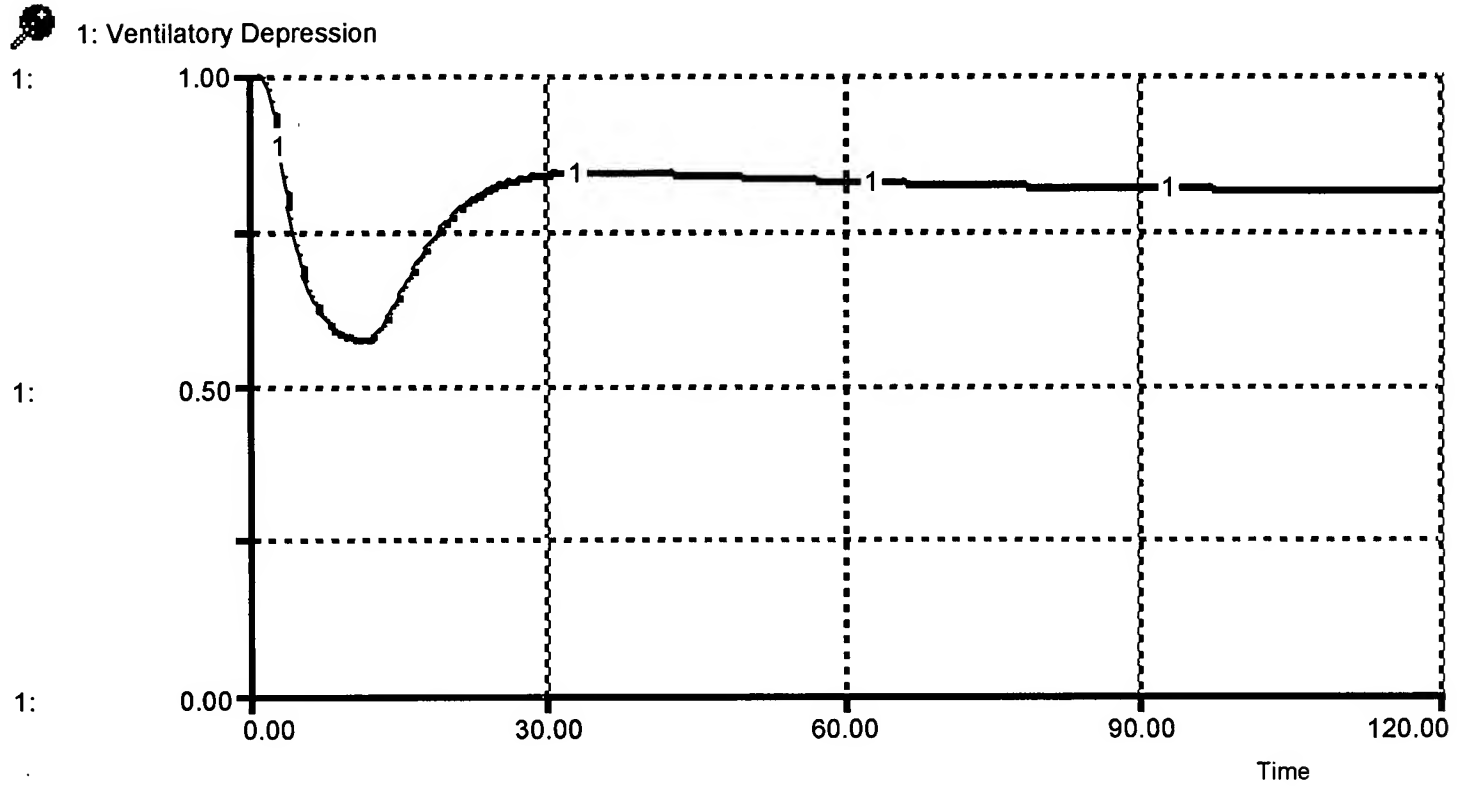


Figure 17A: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is alfentanil, and the slowly acting opioid is morphine.

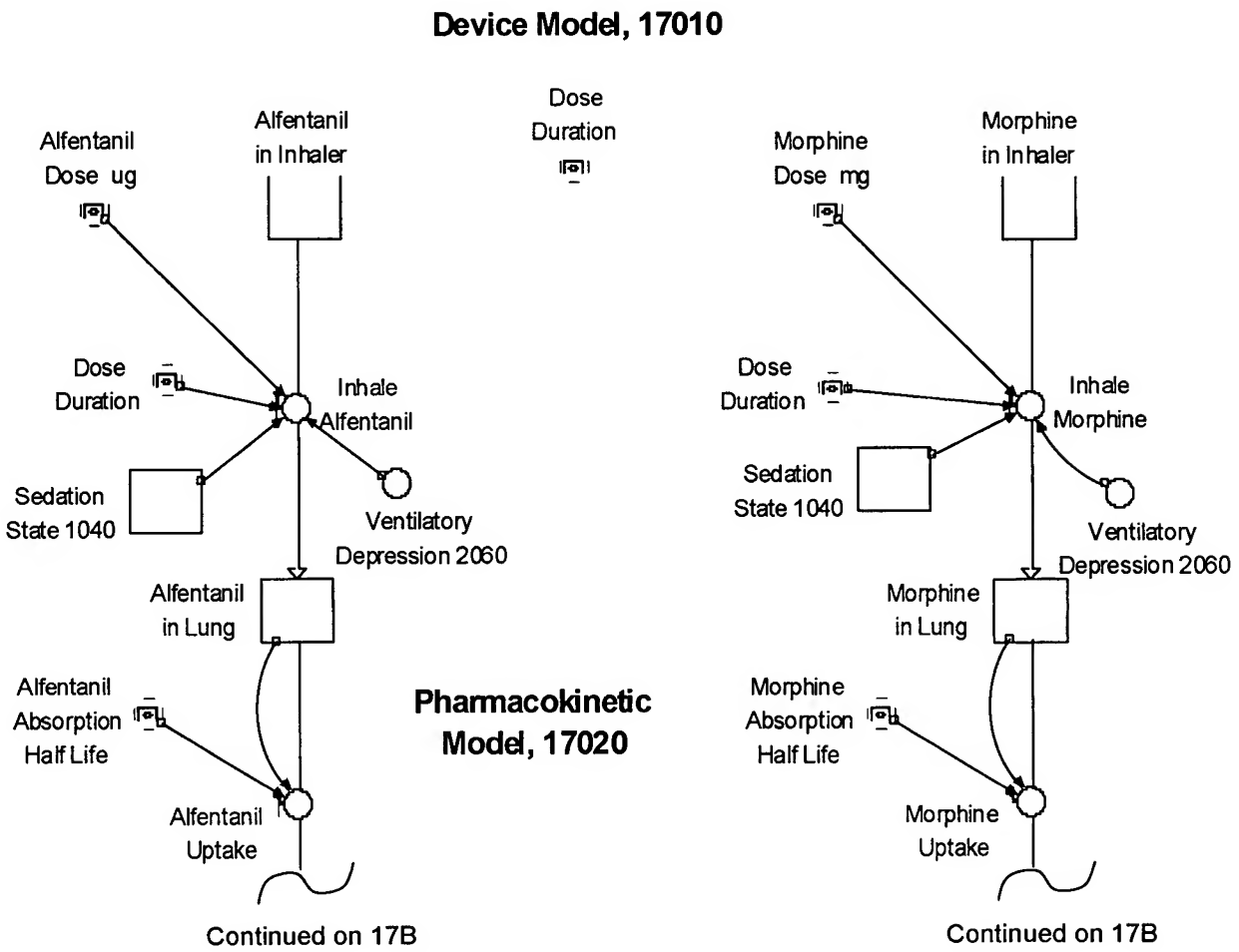


Figure 17B: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is alfentanil, and the slowly acting opioid is morphine.

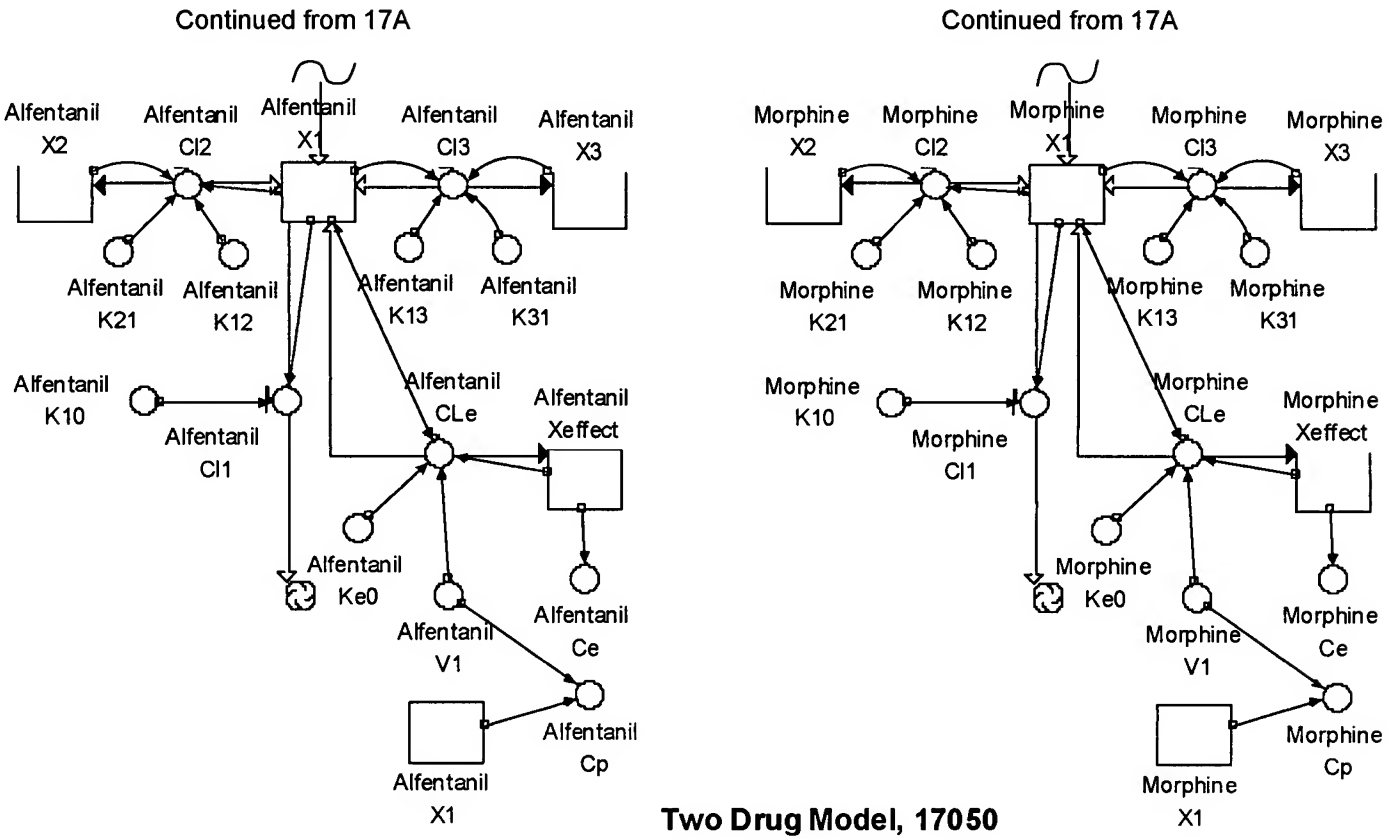
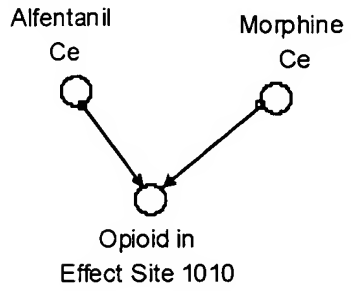
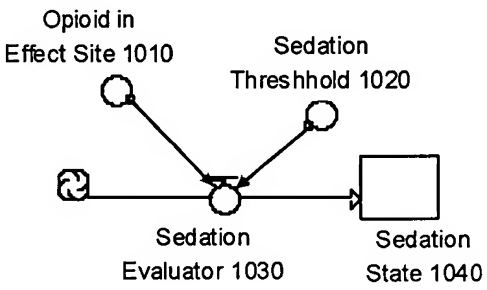


Figure 17C: The elements of the invention, wherein two opioids are administered through inhalation, and the rapidly acting opioid is alfentanil, and the slowly acting opioid is morphine.

Two Drug Model, 17050



Sedation Model 5040



Ventilatory Depression Model 5030

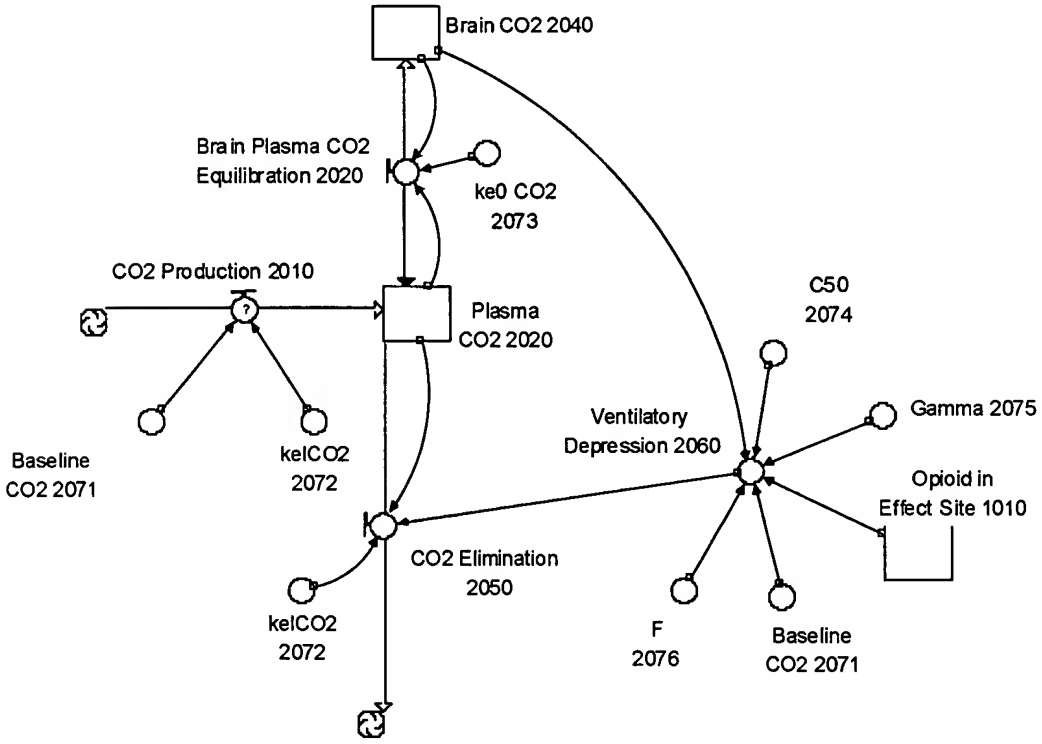


Figure 18: Alfentanil, morphine, and combined opioid effect site concentrations.

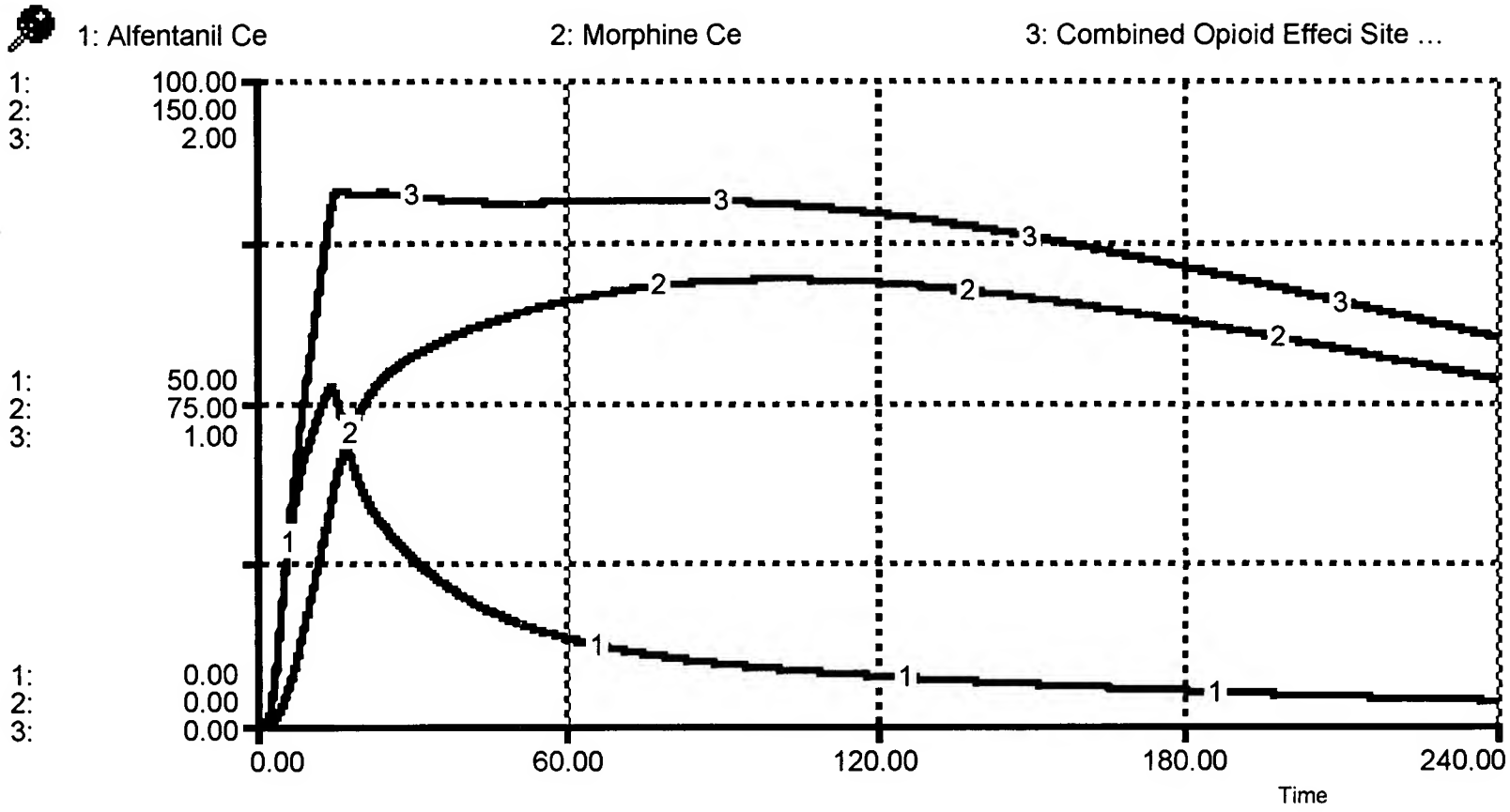
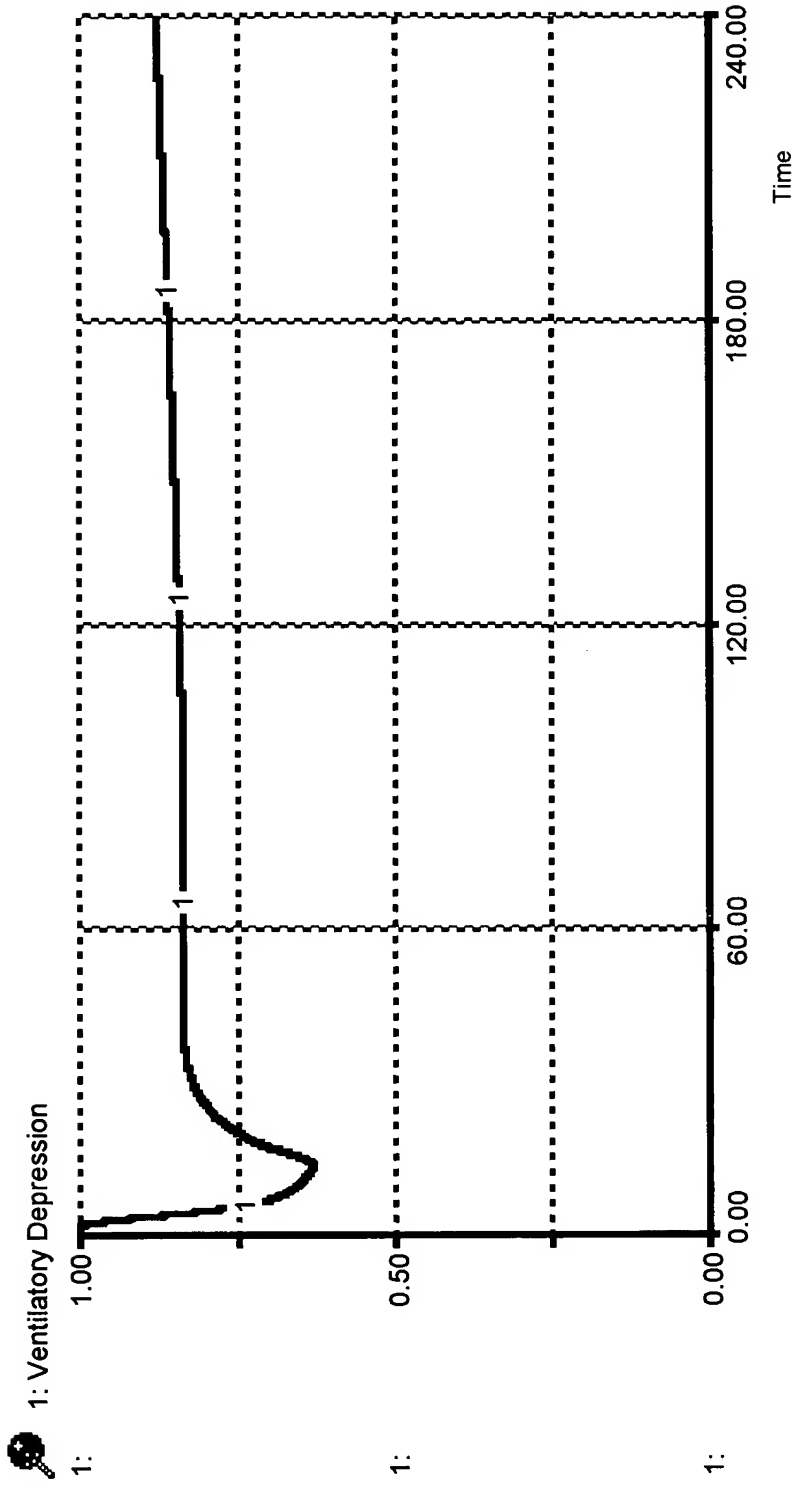


Figure 19


1: Ventilatory Depression
1.00
0.50
0.00
0.00
60.00
120.00
180.00
240.00
Time

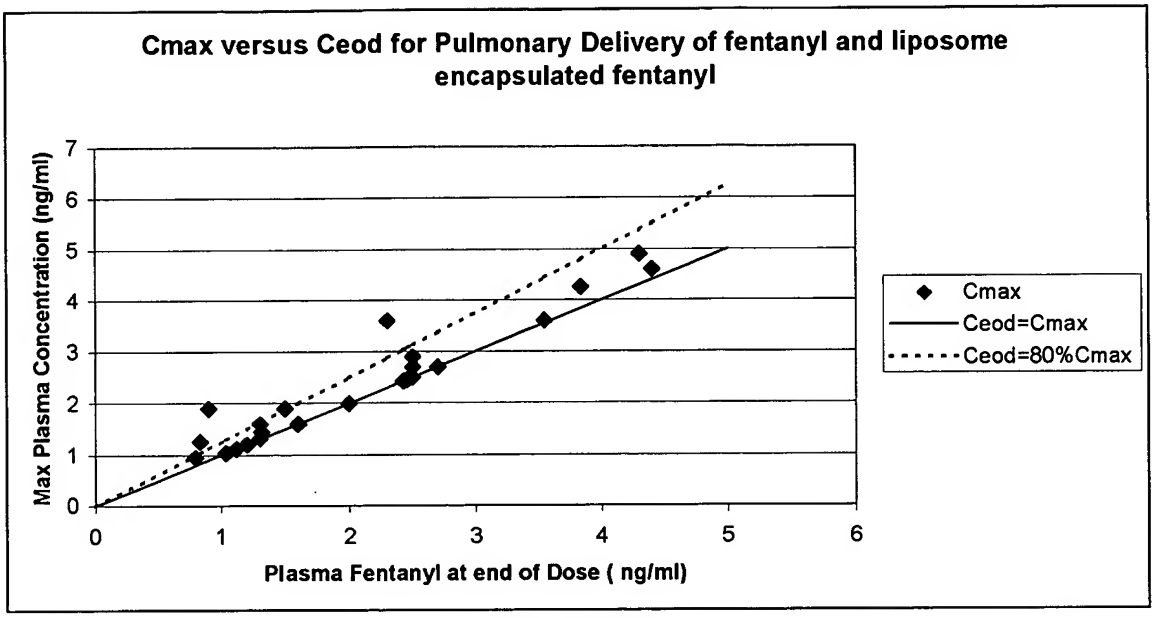


Figure 20A

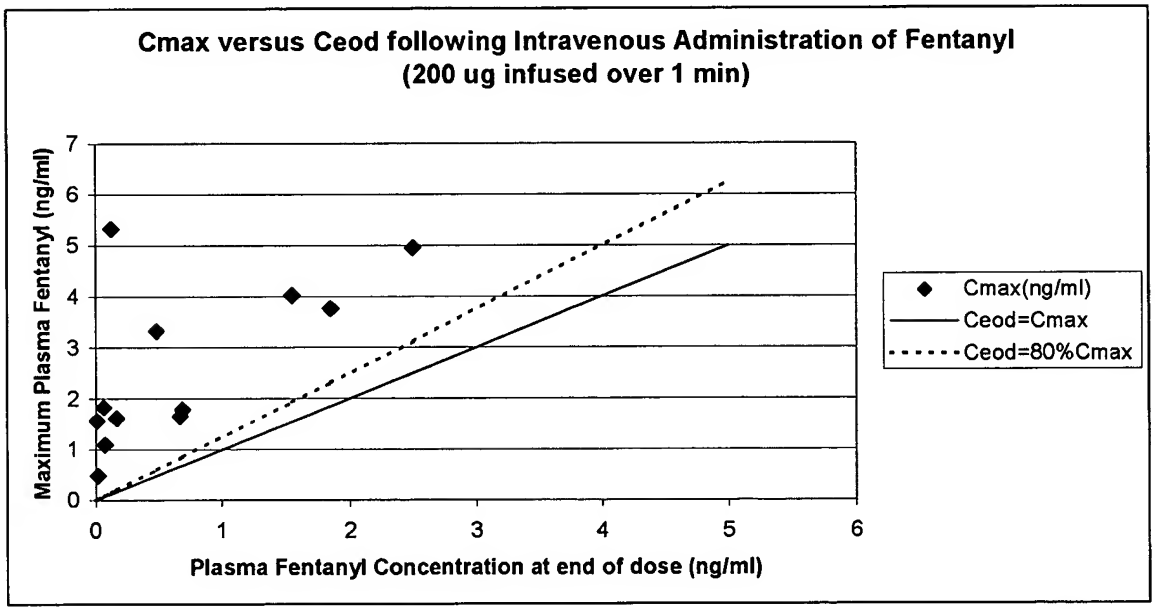


Figure 20B

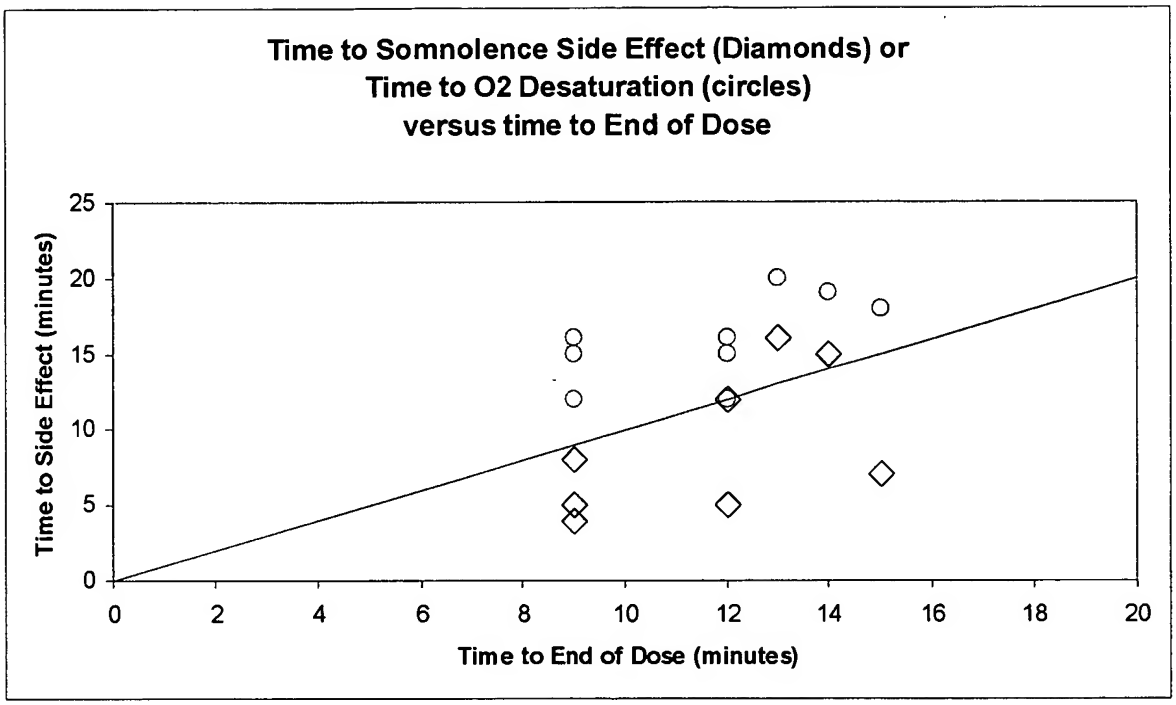

Time to Somnolence Side Effect (Diamonds) or
Time to O2 Desaturation (circles)
versus time to End of Dose
Time to Side Effect (minutes)
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
18
20
Time to End of Dose (minutes)

Figure 21

Figure 22: Correlation of side effect to toxic event

No side effect		Side effect	
N	26	24	
No hypoxia	22	14	36
Hypoxia	4	10	14
Null effect			
No hypoxia	18.72	17.28	36
Hypoxia	7.28	6.72	14
P value	0.038653124		